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ABSTRACT

Research was reviewed on the current status of phenylketonuria, an hereditary amino acid metabolic disorder that can cause severe mental retardation, physical complications, and emotional difficulties if not detected and treated early in childhood. A majority of the research cited was published in the 1960's. Topics covered were: discovery of phenylketonuria; etiology; incidence; clinical syndrome; possible resulting mental retardation; frequent common physical characteristics; possible resulting neurological disorders; detection techniques through urine, blood, fluorometric, and chromotographic screening tests; considerations on dietary treatment; usual positive effects of treatment; treatment problems concerning acceptance of treatment by parents, acceptance by child himself, and regular medical surveillance; and anticipatory and corrective measures for prevention of phenylketonuria. A bibliography of about 70 documents and a listing of states having mandatory screening laws were included. (CB)

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# A Current Look at Phenylketonuria (PKU)

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## Abstract

A current review of data on the subject of phenylketonuria which, if untreated, usually causes severe mental retardation, is presented. Discussed are its discovery, etiology, incidence, the effects and problems of treatment, prevention, and suggested areas of needed research.

The hereditary pattern of the disease, the biochemical processes of normal and abnormal metabolism, and a listing of states having mandatory screening laws are included.

Phenylketonuria (PKU), a hereditarily-transmitted error of metabolism, claims an unparalleled position in the field of mental retardation. Screening techniques leading to early detection and dietary treatment of the abnormality alter favorably the course of severe mental retardation, physical complications, and emotional difficulties commonly associated with the untreated condition.

## Discovery

The identification of this inborn metabolic error occurred less than four decades ago. A Norwegian mother of three children noticed a persistent musty odor associated with her two mentally retarded children. So fetid was the noxious smell that the children's father could not remain in the same room with them if their diapers were wet. To seek help for the children and to learn the cause of the peculiar aroma the mother's search led her from one doctor to another over a span of several years.

In 1934 the problem aroused the interest of an Oslo physician and biochemist, Dr. Asbjorn Fölling, whose examination disclosed that specimens of both children's urine produced an uncustomary green color in reaction to a ferric chloride solution. Dr. Følling proved that this was caused by the excretion of phenylpyruvic acid into the urine.

## Etiology

Phenylketonuria, an amino acid metabolism disorder, is an

example of a recessive Mendelian trait. It is estimated that one in every 50 to 70 persons carries the defective, non-sex-linked gene ((Centerwall and Centerwall, 1965; Woolcott, 1964). If pregnancy occurs between two carriers and the child receives two of the defective genes it will result in phenylketonuria. According to Mendelian theory, in a classical phenylketonuric family of six, the normal parents are each heterozygotes. The children from two such parents can be noncarriers, or carriers like their parents, or receive two abnormal genes and have phenylketonuria. Thus, each pregnancy has a one in four chance of resulting in a phenylketonuric child and a three in four chance of resulting in a phenotypically normal child.

The pathogenesis of the relatively rare malady of phenylketonuria ensues from a deficiency of phenylalanine hydroxylase, the liver enzyme responsible for the conversion of phenylalanine to tyrosine. In patients with PKU, serum phenylalanine levels may reach as high as 60 mg / 100 ml. (The normal level is 1 to 3 mg / 100 ml.) and large quantities of phenylpyruvic acid, phenylalanine, and phenylacetic acid are spilled into the urine. The clinical features of the disease appear to result from the excess accumulation of phenylalanine in blood and spinal fluid and the inhibition of the normal conversion of tyrosine to melanin. It is generally believed that prior to its eventual secretion into the urine the elevated serum phenylalanine level is the direct or indirect cause of the mental retardation and the developmental deficits. The normal metabolism of phenylalanine, an amino acid

essential for growth and maintenance, and the abnormal process which occurs in phenylketonuria is shown in Figure 2 (Oberman, 1965).

## Incidence

The incidence of phenylketonuria has been assessed by epidemiological surveys conducted among newborn, school age, or institutionalized populations in various countries of the world. Probably owing to the fact that the first children afflicted were found in Norway, Sweden, and England, and the physical characteristics of these patients with blonde hair and blue eyes resembled so much the Nordic types, the feeling of many researchers was that the disease was restricted to Northern European nations and their progeny in countries like the U.S.A., Australia, and Canada (Friedman, 1967). More recent research, however, dispelled the veracity of the conclusion that phenylketonuria was nonexistent among non Caucasian populations.

A survey of the racial and geographical distribution of PKU by Friedman showed it to be a universal phenomenon. Certain national and racial groups showed apparent variations in susceptibility, although the results may be due to differences in sampling techniques. As screening programs improved the incidence of PKU seemed to rise. For example, as a result of a mass screening program of newborn infants, the incidence of PKU in England appeared to increase from one in 25,000 to one in 10,000 (Hudson, 1967).

Northern Europeans have consistently shown higher PKU ratios than semitic, Negro, Oriental, or American Indian populations. A recent nationwide screening program in Ireland (Cahalane, 1968) showed a frequency of one in 4,842, an unusually high incidence when compared with the estimate of PKU among Negroes of one in 100,000 (Epps, 1968) or among Ashkenazi Jews living in Israel in which no cases were found in random newborn screening (Cohen and Szeinberg, 1968). The data suggest that there are perhaps a greater number of carriers of the defective gene in certain geographical areas than the one in 50 to 70 originally estimated. Or it may be that the screening programs in many nations have yet to reach the level of efficiency that has been attained in areas where PKU appears to be unusually prevalent. As it has been commented, our knowledge of where phenylketonuria occurs is largely commensurate with where it has been looked for. There has been, in fact, a case of PKU reported recently in a mule deer (Studien et al., 1968) which illustrates that the genetic mutation is not peculiar to homo sapiens.

Centerwall and Centerwall (1965) stated that assuming the incidence of phenylketonuria in the general population is one in 10,000 then it can be determined that one in 50 of the general population is a carrier of the disease. Woolcott (1964), basing the probability of carriers of the recessive trait to be one in 70, postulated that the chance of two carriers marrying each other was approximately one in every 5,000 marriages. If each of these couples had four offspring, then one of the 20,000 children would probably have phenylketonuria.

Morton (1961) observed that rare recessive diseases such as phenylketonuria, albinism, and amaurotic idiocy showed a marked excess of consanguineous parentage. A carrier of a rare gene is unlikely to marry another carrier if mating is at random, but this is more likely to happen if he marries a relative. Penrose (1949) noted that the evidence of inbreeding carries more weight in the diagnosis of a recessive defect than the estimation of Mendelian ratios. Centerwall and Kapur (1964) stated that PKU was found in families originating from only two geographical pockets on the India Mysove State in South India and in West Pakistan where there are relatively high rates of consanguineous marriages.

## Clinical Syndrome

The symptomology of phenylketonuria, although not marked by a specific behavior pattern in every individual, may be categorized under three common areas of clinical manifestation: 1) mental; 2) physical; and 3) neurological.

## Mental

Mental retardation, ranging in degree of severity from mild to severe, is an almost unflagging manifestation of untreated phenylketonuria. Although the newborn infant appears to have normal intellectual endowment, the inherited metabolic defect in phenylketonuria causes the phenylalanine ingested in such dietary proteins as milk or meat to reach toxic levels which

are causally linked to the subnormal developmental symptoms in phenylketonuric infants, particularly mental impairment. The deterioration of intellect varies among individuals. A few rare exceptions have been found of untreated PKU children having intelligence above the mentally defective range (Knox, 1960; Cowie, 1951; Blainy and Guilford, 1956; Sutherland, et al., 1960; and Penny and Fischler, 1966). The majority, however, have I.Q.'s below 50 and are commonly classified intellectually either as having profoundly or severely retarded mentality.

Generally, the pathognomic signs begin to appear about three or four months of age. A state of passive apathy becomes evident. Except for fright emotional responses are blunted and a lack of interest is displayed in their environment. Thereafter, development is slowed down or arrested until two or three years of age. Verbal behavior, often absent or slow to develop, is frequently replaced by peculiar vocal utterances. Concentration is poor and behavior is erratic. Without apparent reason mood swings may occur in which listless or euphoric behavior suddenly changes to bursts of hyperactive irritability, destructiveness, and confusion. The deviant behavioral symptomatology found in untreated phenylketonuric children frequently shows striking similarity to that found in childhood schizophrenia or in infantile autism (Friedman, 1965; Benda, 1960; Dodson, 1964).

Since a marked change in behavioral pathology occurs under dietary treatment in phenylketonuria there is promise that by

understanding the biological mechanisms responsible for activating the deviant behavior patterns may further understanding of psychotic behaviors.

## Physical

Phenylketonurics do not form a group as physically well-defined as cretins or mongoloids but several common characteristics have been found among them. The majority of the patients have blonde hair, blue eyes, and lightly-pigmented skin. The diluted pigmentation is not a constant feature of the defect, however, and has been reversed by phenylalanine restriction or tyrosine supplementation (Menkes, 1967). Among a group of 31 PKU patients described by Koch et al. (1964), 16 had brown hair, 9 were blonde, 5 had red hair, and one was brunette. There are, nevertheless, striking examples of blonde phenylketonurics in darkly-pigmented families of Spanish or Sicilian descent (Josephy, 1948; Jervis, 1954). A case of a mulatto with blonde hair and blue eyes was reported by Stadler et al. (1956).

The phenylketonuric child's physical development is generally good although, except for large shoulder width, his stature is often smaller than average expectancy. If untreated, there is generally a developmental lag in age for sitting alone and for walking. Facial features are often of remarkable regularity. Wide spacing of the upper incisors has been described as typical of the disease (Cowie, 1951) and is observed in a good percentage but not in the

majority of patients. Skin diseases, such as dermatitis and eczema, are commonly present as is anemia and bone marrow abnormality.

A forward leaning posture, a rigid gait, and elaborate playing with fingers and hands as is observed in autistic children are stereotyped behaviors associated with the PKU child.

The one symptom that has repeatedly been observed in relation to phenylketonuria is a pungent odor of remarkable stability that is described variously as "musty" in character, "mousy," or "barnlike." Phenylacetic acid can duplicate the odor.

## Neurological

Approximately one fourth of the children with phenylketonuria suffer from epileptic seizures of the grand mal type (Jervis, 1963). The onset of the seizures is at about age two. As the child grows older the severity of the seizures lessens, often to disappear in adulthood.

Positive Babinski and ankle clonus, and signs of upper motor neuron damage may be found in severe cases. Mild muscular rigidity and hypotonicity with sluggish deep tendon reflexes is noted often. Rapid, rhythmical tremors may also be evidenced. Profoundly retarded phenylketonurics show motor impairments in combination with some degree of microcephaly.

Sexual development is usually normal, and the phenylketonuric is capable of reproduction.

## Detection

Several tests are available for the identification of phenylketonuria. The techniques include urine, blood, fluorometric, and chromotographic screening devices.

The urine tests include the Ferric Chloride Test, the Diaper Test, the Filter Paper Test, the Phenistix Test, the Dinitrophenylhydrazine Test, and Chromatographic Tests.

The Guthrie or Microbiological Inhibition Assay was introduced in the early 1960's to compensate for the deficiencies of urine screening programs. False negatives resulted, at times, when the urine specimen tested was not a fresh sample or if the phenylpyruvic acid in the urine was below the serum level of 15 mg / 100 ml. (Cunningham, 1971). The Guthrie Inhibition Assay, a blood test, is especially valuable because it will demonstrate elevated phenylalanine blood levels below 20 mg / 100 ml.

The fluorometric method has even greater precision than the Guthrie technique for the determination of phenylalanine in serum (McCaman and Robins, 1962). The fluorometric test, which is based on the enhancement of the fluorescence of phenylalanine in the blood sample through the addition of certain chemical substances, is claimed to be sensitive to low phenylalanine levels of 4 mg / 100 ml. which would not be identified by the Guthrie technique

et al.,
(Irwin, 1964).

Detection of phenylketonuria by the various screening devices is usually contingent on specific procedures being followed. When they are not reliability of the results becomes questionable and the possibility of false negative diagnoses increases. Since phenylpyruvic acid is not always detectable in the urine at birth Pick (1965) suggested retests four to six weeks after birth if the baby failed to thrive, when there were signs of eczema in the newborn period, and when there was a history of mental retardation in the family.

Chromatographic tests, because of their lack of sensitivity to the normal ranges of phylalanine levels and the problems of control related to the achievement of reliability, make their use unpopular even though they potentially are able to detect a broader range of abnormalities.

More precise descriptions of the methods for detection of PKU can be found in the Cunningham (1971) article and in Chapter 7 of Phenylketonuria, edited by F.L. Lyman (1963).

Programs for the detection of PKU in newborn infants received considerable impetus over the last twenty years. The Children's Bureau of the U.S. Department of Health, Education, and Welfare contributed funds to states for initiating screening programs and for providing treatment services for those affected

with phenylketonuria. In 1966 it was reported that 25 states had mandatory screening laws and that the screening of newborns was encouraged in 7 other states (Snodgrass, 1966). Less than a year later Mann and Champion (1967) reported that the number of states having passed PKU legislation had risen to 38 with 4 more expecting laws to be passed in the next session of their legislature. The author concluded a survey of the states with mandatory screening laws and found that of the 50 states had instituted such legislation (Fischer, 1971). Of the states without mandatory screening states had voluntary programs for screening newborns which were claimed to be effective (see Table 1).

In addition to the screening of newborns some states have initiated pilot testing programs among school-aged children. In a California study 68 phenylketonuric children were located of whom 26 were newly identified and 42 were known cases (Williamson et al., 1968).

## Treatment

That irreversible brain damage can be prevented or modified by restriction of phenylalanine in the diet has made the disease of phenylketonuria a unique entity in the field of mental retardation. Although dietary management is not yet a panacea, the positive effects which accrue to the child from proper maintenance of the diet far outweigh its disadvantages.

An apparently critical variable is the time at which treatment is initiated. With the ingestion of proteins from milk, the newborn infant with phenylketonuria, because of his metabolic defect, build's up serum phenylalanine levels at about 20 times the normal rate. The high concentration of phenylalanine in the serum is generally believed to be the causative factor of the brain damage and the resultant mental deficiency.

Although there are variations in individual tolerances of serum phenylalanine levels most researchers agree that in order for treatment to counteract effectively the damage to the brain during its early developmental phases the infant should be started on the diet as early after birth as possible but no later than three months of age (Kang et al, 1965; Berry et al., 1966, 1967; Oura, 1964; Berman et al., 1969; Cohen et al., 1969).

Retarded phenylketonurics who are detected and started on a low phenylalanine diet at an older age (3 to 4 years of age) do not generally respond to intellectual treatment. Kleinman (1964) stated that the data on late-initiated treatment indicate that the considerable variation among phenylketonurics in response to treatment may reflect individual rates of permanent damage. He noted that the decline in I.Q. occurs largely in the early years of life but continues to decline more slowly until 8 to 14 years of age, perhaps because the brain is more vulnerable to damage from high phenylalanine levels during its rapid development in

early childhood; or that brain damage is associated with high levels of concentration of phenylalanine which chiefly occurs in the neonatal period.

The regimen low in phenylalanine is aimed at maintaining the amino acid balance necessary to promote good nutrition and normal body growth. Commercially-prepared synthetic products which provide amino acids with little phenylalanine are the mainstay of the diet. Lofenalac, an American-made product with a pleasant nut-like flavor, contains fat, carbohydrate, and certain minerals and vitamins incorporated with the low-phenylalanine casein hydrolysate. Because of its low phenylalanine content the diet may be supplemented with low-protein vegetables and fruits for variation.

Davens, et al, (1965) commented on the discrepancies of opinion which exist regarding the treatment of phenylketonuria. The enthusiasts of the treatment programs say that with adequate mass screening, diagnosis, and early treatment, phenylketonuria can be eliminated as a cause of mental retardation; the doubters believe that there is need to improve screening procedures and that the efficacy of treatment leaves much to be desired.

## Effects of Treatment

Researchers have found that the effects of treatment vary depending upon the age at which treatment was initiated. Ouna (1964) studied three cases in which treatment started at the age of one and a half months, ten months, and eleven months of age. A DQ

of 91, 104, and 91 respectively was maintained. Patients whose treatment started between one and three years of age showed definite retardation with small success in the rise of IQ even on the diet. Treatment started at age five or later showed no essential change of IQ in the retarded patients. All patients with grand mal epileptic seizures were relieved of the seizures when placed on the diets without anticonvulsant medication. Ouza concluded that considerable improvement in the behavior pattern of the patients was evidenced even when there was no rise in IQ. They became less irritable, more obedient, and were more responsive to the environment.

Berry et al. (1967), in a longitudinal study of 27 phenylketonuric patients at Children's Hospital in Cincinnati, showed that optimal growth was obtained by all but one child in the earliest treated group (before three months of age); those patients treated later than three months of age for a period of one to six years showed deficits in language abilities and behavior and had a higher frequency of neurological abnormalities compared to children treated at less than three months of age. Normal intelligence was maintained or attained if onset of treatment was from three days to eleven weeks of age.

Hsia (1966) did not find that treated phenylketonuric patients attained the normal ultimate in intelligence even when early dietary management was initiated, but showed signs of improvement if treatment was begun before age three.

Kang (1965) evaluated infants with phenylketonuria over a three-year period. The mean I.Q. for subjects treated at a mean age of 3.6 weeks was 94. The group treated after six months had a mean I.Q. of 59.3 which was significantly less than the early-treated group.

Two British authors presented case material to support testing older children for phenylketonuria. Budding (1965) reported a case in which the disorder was discovered in an eight-year-old boy who had an I.Q. of 68 and displayed erratic behavior patterns. His I.Q. raised to 85 by age 13 and his behavior stabilized on a regime of strict diet and remedial education. Moncrieff (1965) noted that the failure to test routinely for phenylketonuria among older children may have arisen from the misunderstanding that nothing could be done for them, but experience has shown a dietary treatment response of 15 to 20 I.Q. points in some older children.

## Problems of Treatment

Dietary treatment of the disorder, while generally highly effective, is associated with several problems. Serum levels must be determined regularly for excesses or deficiencies of phenylalanine so the diet can be adjusted accordingly. Protein deficiency from overrestriction of phenylalanine can lead to symptoms of malnutrition.

Delaitre and Perreau (1965) enumerated three problematic areas:

1) acceptance of the treatment by the parents; 2) acceptance by the child himself; and 3) regular medical surveillance. Schild (1964) stated that the rigid adherence to dietary treatment may create anxieties within the family. The child often develops negative attitudes toward his diet, and his varied reactions may become stressful and anxiety-provoking for his parents. As the child grows older it often becomes difficult for the parents to maintain his somewhat monotonous, distasteful diet which, among its other shortcomings, has no real palatable substitute with consistencies similar to actual bread or toast. "Sneaking" nondietary foods often results which, in turn, aggravates the stressful family situation and creates problems for the attending physician trying to stabilize the blood phenylalanine levels.

Termination of dietary treatment of phenylketonuria at a time when normal mentality and development can be assured adequate maintenance is still a matter of controversy. Knox (1960) estimated the frequency of patients with phenylketonuria with high-grade intelligence as 2.5 per cent. Thus, Horner et al. (1962) thought it conceivable that, if the mental retardation and the metabolic abnormality represent the pleiotropic expression of the same gene, a phenylketonuric child may reach the same level of mental function without dietary treatment. Solomons et al. (1966) found no deleterious effects in seven children aged 9 months to 7 years, 8 months after a mean cessation of diets of seven and one-half months. They concluded that termination of the diet after

the age of 6 years was safe and seemed to produce improvement in behavior, school performance, and in the emotional climate of the family.

Kang et al (1970), who concluded that it safely can be assumed that the occurrence of phenylketonuria with normal intelligence is extremely rare, found that more than half of the late-treated patients achieved significant gains during the course of their treatment. When dietary therapy was concluded there was no evidence of deterioration in 11 patients after a six-year follow up study.

As Moncrieff (1964) observed the problem of when to stop the diet in phenylketonuria is an agonizing one. Centerwall et al., (1961) warned that even if I.Q. did not decrease with termination of dietary treatment a return of features such as irritability and clouding of affect could have an adverse effect on the child's development. McBean and Stephenson (1968) suggested that on the basis of the findings of their studies of results of stopping the diet that in some cases it was not possible to escape the conclusion that intellectual growth was related to dietary control, and not to factors such as mental stimulation, as suggested by Bessman (1966). They suggested that physicians who believed that the diet should be stopped in the early school years should only allow this in the context of a controlled trial, employing a battery of psychological tests.

A statement on treatment of phenylketonuria outlined by the Committee on the Handicapped Child (1965) commented that an objective evaluation of the results of dietary treatment of children with PKU must take into consideration a multiplicity of uncontrolled variables affecting the outcome. Included are the differing initial levels of intelligence and phenylalanine tolerance in each child, the differing heredities of each child (even in the same family), and the differing abilities and motivations of parents in maintaining the diet.

At the present stage of knowledge dietary treatment has not reached the stage of a cure for all the ills of the metabolic defect of phenylketonuria, but the advances stand out in the field of mental retardation as exemplary in ameliorating the deficits associated with abnormalities which are organically based. The need to ascertain more exactly the extent to which dietary restriction of phenylalanine is beneficial to the well being of the phenylketonuric individual is still needed. The ability to terminate the diet safely would have obvious beneficial effects for the child and for his parents.

## Prevention

Measures for the prevention of phenylketonuria or of its effects can be categorized as either anticipatory in nature or as corrective. Anticipatory measures precede the birth or the likelihood of the birth of a metabolically abnormal and/or mentally retarded child, while corrective measures are aimed at improving the impairment which results from the disease.

Since phenylketonuria is inherited as a Mendelian recessive both parents must be carriers in order that a pregnancy which could possibly result in a phenylketonuric child could occur. If one parent can be shown to be genetically normal then the diagnosis of PKU in the child can be excluded (Schneider and Garrard, 1966).

One way of preventing phenylketonuria, therefore, would be to dissuade carriers from marrying. To accomplish that end several interrelated approaches were proposed: 1) the need to identify carriers; 2) the establishment of PKU registries, and 3) genetic counseling. The suggestion of Bessman (1965) to devise a means to identify carriers of the defective gene can now be implemented by a simple phenylalanine tolerance test, as heterozygous carriers for PKU have plasma phenylalanine levels twice those of normal controls (Kirman, 1965; Hsia, et al 1956; Perry, et al 1967).

As another aspect of preventative medicine Scott (1966) expressed the need for local PKU registers for carriers of the gene. While the idea met with some resistance, perhaps because of the stigma attached to being listed as a carrier of a defective gene, PKU registries are now a reality in many states.

A PKU registry can be utilized to facilitate genetic counseling for treated phenylketonurics of child-bearing age, for unmarried carriers, and for heterozygotes who are married to each other. Kirman (1965) stressed the importance of genetic counseling

for phenylketonurics who received the benefits of treatment in infancy. Unlike most untreated patients of the metabolic anomaly of yesteryear, they have good preservation of intelligence and are eligible for marriage and reproduction. With the increased risk of a homozygote and a heterozygote marrying, the chance of the progeny being affected is greater also.

Marriages of heterozygous carriers have had the occurrence of the birth of a second child with PKU into the family which emphasizes the importance of parental counseling among these individuals (Scott, 1966).

When elevated serum phenylalanine levels occur during pregnancy in PKU carriers or in homozygotes permanent neurological damage to the fetus may result (Kang and Paine, 1963; Cass and MacCready, 1964; Woolcott, 1964). Some cases of mental retardation of unknown etiology may be related to such factors. Administration of a diet with a low phenylalanine concentration during pregnancy may avert the possible mentally deficient status of the newborn child. To prevent this occurrence Coffelt (1964) recommended the testing of all mothers of retarded children.

Prenatal testing of phenylalanine tolerence levels of all pregnant women could be a more efficacious means of locating carriers and unsuspected phenylketonurics. Initiating dietary treatment during pregnancy could then inhibit or arrest the damage to the fetus.

Experimental research in which phenylketonuria has been produced in monkeys and rats (Waisman, 1963) may lead to a better understanding of the biochemistry of the mental defect in human beings. Meister (1963) emphasized that new ways of correcting the metabolic block in phenylketonuria should constantly be borne in mind, and research should be directed toward the possibility of substituting the missing enzyme.

Considering the remarkable scientific progress made in less than forty years in the control of phenylketonuria in the United States and abroad, the future holds great promise for the amelioration of the problems of disease and mental retardation.

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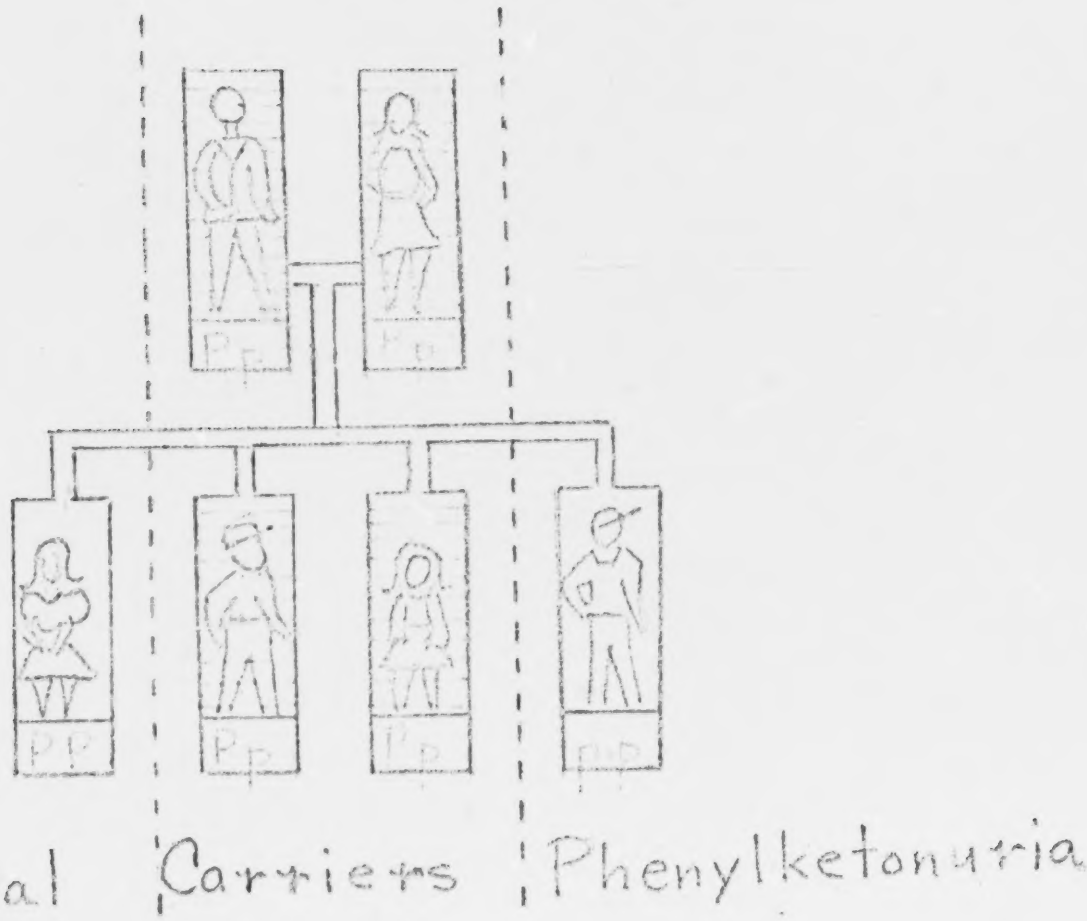
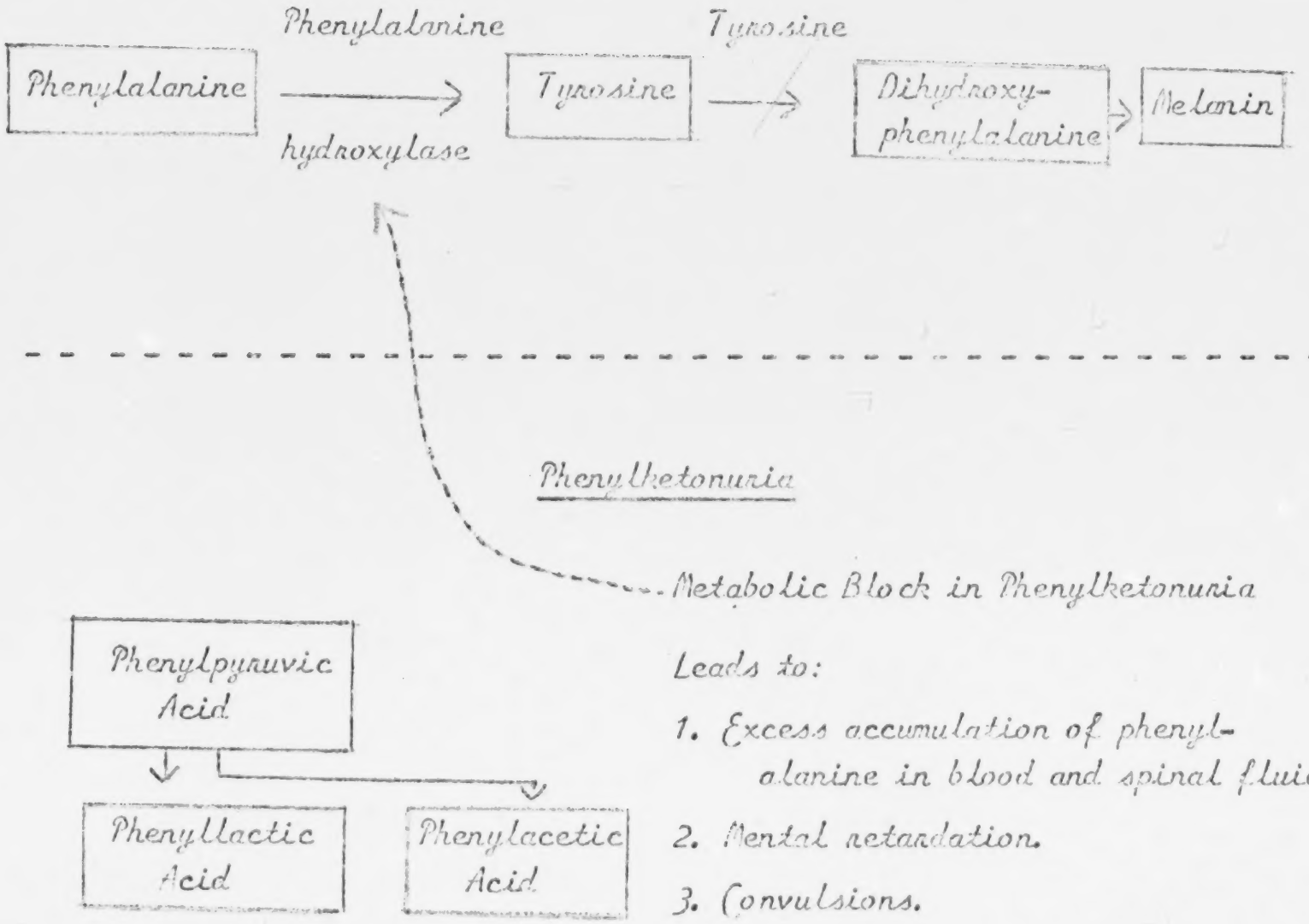
# Appendix

Figure 1. Inheritance Pattern for Phenylketonuria.




(After Centerwall and Centerwall, 1965).

Figure 2. The Normal Metabolism of Phenylalanine and the Abnormal Metabolism of Phenylketonuria.




Leads to:

1. Excess accumulation of phenylalanine in blood and spinal fluid.
2. Mental retardation.
3. Convulsions.
4. Behavioral abnormalities.
5. Inhibition of conversion of tyrosine to melanin.
6. Unusually lightly pigmented hair and blue eyes.

(From J. Wm. Oberman, "The Pathogenesis of PKU". GP, 1965. Used by permission of American Academy of General Practice, Publisher.)

Table 1. States with Mandatory Legislation for Screening Newborns for Phenylketonuria and the Date the Law Became Effective.

| | | | | | |
|---|---|---|---|---|---|
| 1. | Alabama | 1965 | 26. | Montana | 1965 |
| 2. | Alaska | 1967 | 27. | Nebraska | 1967 |
| 3. | Arizona | no law | 28. | Nevada | 1967 |
| 4. | Arkansas | no law * | 29. | New Hampshire | 1965 |
| 5. | California | 1965 | 30. | New Jersey | 1964 |
| 6. | Colorado | 1965 | 31. | New Mexico | 1966 |
| 7. | Connecticut | 1966 | 32. | New York | 1965 |
| 8. | Delaware | no law * | 33. | North Carolina | 1965 |
| 9. | Florida | 1965 | 34. | North Dakota | 1967 |
| 10. | Georgia | 1966 | 35. | Ohio | 1966 |
| 11. | Hawaii | 1965 | 36. | Oklahoma | 1965 |
| 12. | Idaho | 1965 | 37. | Oregon | 1963 |
| 13. | Illinois | 1965 | 38. | Pennsylvania | 1965 |
| 14. | Indiana | 1965 | 39. | Rhode Island | 1964 |
| 15. | Iowa | 1965 | 40. | South Carolina | 1965 |
| 16. | Kansas | 1965 | 41. | South Dakota | no law |
| 17. | Kentucky | 1966 | 42. | Tennessee | 1968 |
| 18. | Louisiana | 1964 | 43. | Texas | 1965 |
| 19. | Maine | 1965 | 44. | Utah | 1965 |
| 20. | Maryland | 1965 | 45. | Vermont | no law * |
| 21. | Massachusetts | 1963 | 46. | Virginia | 1966 |
| 22. | Michigan | 1965 | 47. | Washington | 1967 |
| 23. | Minnesota | 1965 | 48. | West Virginia | 1965 |
| 24. | Mississippi | no law | 49. | Wisconsin | 1965 |
| 25. | Missouri | 1965 | 50. | Wyoming | no law * |

(Fischer, July 1971)

* voluntary basis.